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MEIOTIC DRIVE AND SEX CHROMOSOME CYCLING

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Abstract.—Sex-linked meiotic drive is found in a broad variety of taxa, including insects, birds, and mammals. In populations of some species, we see four types of sex chromosomes segregating: normal and driving X chromosomes and susceptible and resistant Y chromosomes. A theoretical analysis shows that a stable four-chromosome equilibria is a more common outcome in these systems than previously recognized. Cycling of sex chromosome frequencies and associated changes in the sex ratio are other predicted outcomes. The absence of cycling in nature may be due to migration among populations.

Key words.—Driver, migration, sex ratio, suppressor, X chromosome polymorphism, Y chromosome polymorphism.

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Meiotic drive involving sex chromosomes is well documented in several species of *Drosophila*, in other dipterans, and in a few other taxa including birds and at least one mammal (Hurst and Pomiankowski 1991, table 1; Jaenike 2001). In these taxa, there exist X chromosomes that are overrepresented in sperm, giving rise to a female-biased sex ratio in the population. Such X chromosomes are termed ''driver'' or ''distorter'' X chromosomes (X_d). The X-linked locus (or loci) controlling drive gains a transmission advantage if the total number of daughters produced is higher than for a normal male.

In spite of their transmission advantage, X_d chromosomes are absent from the vast majority of species and, when they do occur, are often found at relatively low frequencies and seem not to increase in frequency over time (James and Jaenike 1990). These observations suggest that X_d chromosomes have a viability or fecundity cost associated with them that offsets their transmission advantage. Fitness costs have been observed in some laboratory experiments (e.g., Curtsinger and Feldman 1980).

In addition to a possible fitness cost associated with X_d chromosomes, evolution at other regions in the genome may also be important in determining their ultimate fate. Once X_d enters a population, the population experiences a female-biased sex ratio. Individuals that overproduce males are then favored (Fisher 1958; Uyenoyama and Bengtsson 1979). Alleles on autosomes that can overcome the ability of X_d to distort transmission should increase in frequency. This would lead to a reduction in drive and perhaps a disappearance of the female-biased sex ratio from the population. When X_d chromosomes are present, Y chromosomes experience a direct transmission disadvantage. Y chromosomes that can overcome drive will have increased fitness due to their direct effect of overcoming drive. Thus, we might expect to find such suppressor Y chromosomes (Y_{sup}) in populations harboring X_d chromosomes. Y_{sup} chromosomes have been found in some species possessing X_d chromosomes but not in others (Carvalho et al. 1997; Presgraves et al. 1997; Carvalho and Vaz 1999; Jaenike 1999).

Because of the many factors that come to bear on the evolution of X_d chromosomes, it is striking that they seem to occur at relatively constant frequency in some populations (see Carvalho and Vaz 1999). Even more remarkable are the populations that harbor X, X_d, Y, and Y_{sup} chromosomes. While a four-chromosome equilibrium is theoretically possible, it occurs in a restricted region of the parameter space (Clark 1987; Carvalho and Vaz 1999). Jaenike (1999) argued that four chromosome polymorphisms arise in populations that are initially polymorphic for X chromosomes. With this assumption the region of the parameter space allowing Y chromosome polymorphism is somewhat less restricted but still quite small (Jaenike 1999).

In this paper, I argue that four chromosome equilibria should be substantially more common than previous work has appreciated. In addition, I describe a cycling dynamic that has been unappreciated in previous work and show that migration between populations may explain why cycling is not seen in nature.

THE MODEL

I assume that X_dY males produce sufficient numbers of sperm to fertilize all ova, such that the effect of the X_d chromosome in X_dY males is only on transmission of the X_d versus Y chromosome. I model this meiotic drive by assuming that an X_dY male produces $(1/2 + d)$ X_d sperm and $(1/2 - d)$ Y sperm ($0 < d \leq 1/2$). I further assume that the X_d chromosome incurs a cost (viability or fecundity) in females. I denote this cost using the parameter t such that X_dX_d females have viability $(1 - t)$ and XX_d females have viability $(1 - ht)$, where h measures the dominance of the X_d chromosome on viability ($0 < t, h \leq 1$).

Males possessing the resistant Y_{sup} chromosome exhibit complete suppression of drive and always show normal segregation. Males carrying Y_{sup} suffer a viability cost equal to s ($0 < s \leq 1$), such that the viability of XY_{sup} and X_dY_{sup} males is $(1 - s)$ relative to XY and X_dY males. For an overview of the selection and drive parameters, see Table 1.

The life cycle begins with adult males and females mating at random. The resulting offspring genotype frequencies are determined by the segregation exhibited by their fathers. Male and female offspring then undergo viability selection dependent on their genotype, attain adulthood, and enter the random mating pool. The cycle then repeats.

With these assumptions, a complete set of recursions can

TABLE 1. Fitness and drive parameters associated with different genotypes in the basic model.

Genotype	Fitness	Gametes			
		X	X_d	Y	Y_{sup}
XX	1	1			
XX_d	$1 - ht$	1/2	1/2		
X_dX_d	$1 - t$		1		
XY	1	1/2		1/2	
X_dY	1		$1/2 + d$	$1/2 - d$	
XY_{sup}	$1 - s$	1/2			1/2
X_dY_{sup}	$1 - s$		1/2		1/2

be written that describe the change in frequency of all the four chromosomes in gametes over a single generation:

$$\bar{w}_{Xf}x'_f = x_f x_m + \frac{1}{2}(1 - ht)[x_m(1 - x_f) + x_f(1 - x_m)], \quad (1)$$

$$\bar{w}_{Xm}x'_m = \frac{1}{2}x_f y + \frac{1}{2}(1 - s)x_f(1 - y), \quad \text{and} \quad (2)$$

$$\bar{w}_Y y' = \frac{1}{2}x_f y + \left(\frac{1}{2} - d\right)y(1 - x_f), \quad (3)$$

where

$$\bar{w}_{Xf} = x_f x_m + (1 - ht)[x_m(1 - x_f) + x_f(1 - x_m)] + (1 - x_f)(1 - x_m)(1 - t), \quad (4)$$

$$\bar{w}_{Xm} = \frac{1}{2}x_f y + \frac{1}{2}(1 - s)x_f(1 - y) + \left(\frac{1}{2} + d\right)y(1 - x_f) + \frac{1}{2}(1 - s)(1 - y)(1 - x_f), \quad \text{and} \quad (5)$$

$$\bar{w}_Y = \frac{1}{2}x_f y + \frac{1}{2}(1 - s)x_f(1 - y) + \left(\frac{1}{2} - d\right)y(1 - x_f) + \frac{1}{2}(1 - s)(1 - y)(1 - x_f). \quad (6)$$

x_f and x_m are the frequencies of the nondriving X chromosome in eggs and sperm, respectively, and y is the frequency of the susceptible Y chromosome in sperm. The primes indicate frequencies in gametes of the next generation.

The location of any population in chromosome-frequency space can be visualized using a two-dimensional square (Fig. 1). A population at a corner of this space is fixed for a single type of X and Y chromosome. A population on an edge is fixed for either a single X or Y and is segregating both chromosomes of the other type (e.g., fixed for X_d, segregating Y_{sup} and Y). A population in the interior is segregating all four chromosomes.

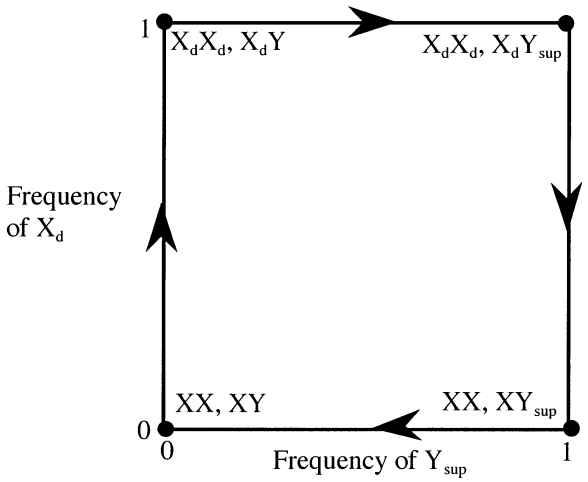

FIG. 1. Four-chromosome frequency space and predicted edge behavior in a population exhibiting an internal equilibrium with small t and s.

RESULTS

Edge Behavior

The behavior of the population along the edges of the chromosome frequency space is easily determined. In a population fixed for X and Y (all females are XX, all males are XY), X_d can invade if its viability cost in heterozygotes is not too great (Table 2). Once it invades, X_d will go to fixation if its viability cost in homozygotes is not too great (Table 2). Thus, a low viability cost driving X chromosome is expected to invade and fix in a population initially fixed for the nondriving X and normal Y. Higher-cost drivers, however, may be able to invade but not go to fixation, resulting in a population equilibrium that is polymorphic for both the driving and nondriving X chromosomes.

Several previous studies have focused on this equilibrium as a possible explanation for populations exhibiting polymorphism in nature (Edwards 1961; Curtsinger and Feldman 1980; Clark 1987; Hurst and Pomiankowski 1991). However, it is straightforward to show that a population at this equi-

TABLE 2. Exact conditions for the invasion of fixation equilibria.

Equilibrium	Introduced chromosome	Condition for successful invasion
X and Y fixed	X_d	$d > ht/(1 - ht)$
X and Y fixed	Y_{sup}	invasion cannot occur
X_d and Y fixed	X	$t < 1/(2 - h)$ and $d < t(1 - h)/[(1 - t) - t(1 - h)]$ or $t > 1/(2 - h)$
X_d and Y fixed	Y_{sup}	$s < 2d$
X_d and Y_{sup} fixed	X	invasion always occurs
X_d and Y_{sup} fixed	Y	$s > 2d$
X and Y_{sup} fixed	X_d	invasion cannot occur
X and Y_{sup} fixed	Y	invasion always occurs

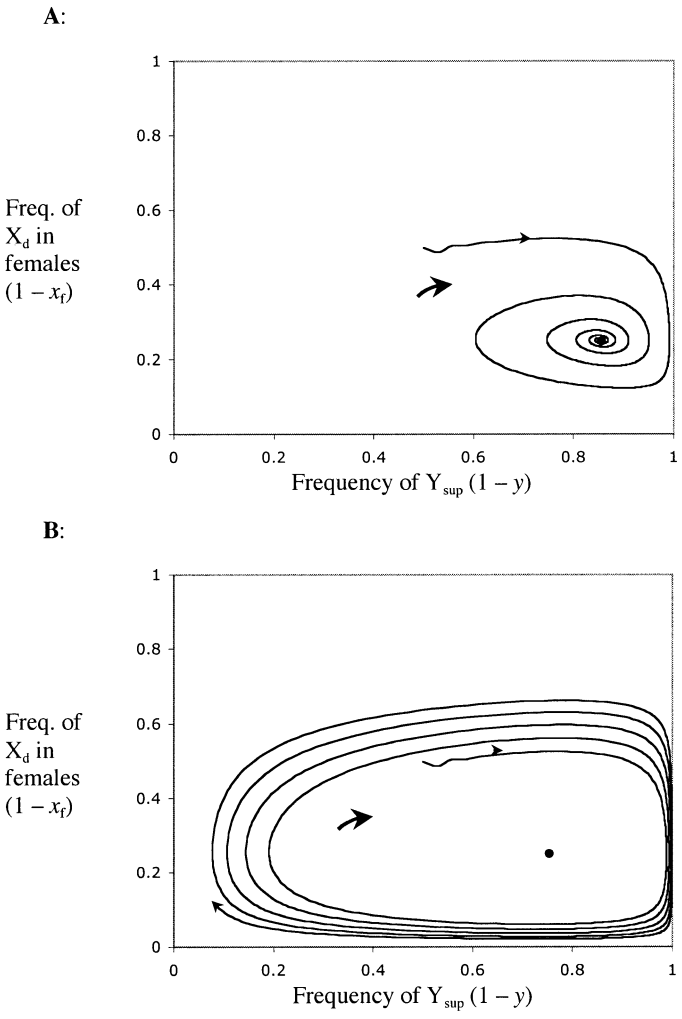

FIG. 2. Expected dynamics with low-cost drivers. The internal equilibrium is shown as a black dot. The line shows the dynamics of a population started with equal frequencies of all four sex chromosomes and followed for 1000 generations. (A) Population exhibiting a stable internal equilibrium ($h = 0.1$, $t = 0.1$, $s = 0.1$, $d = 0.2$). Internal equilibrium is $\hat{y} = 0.145$, $\hat{x}_f = 0.75$, $\hat{x}_m = 0.738$. (B) Population exhibiting an unstable internal equilibrium ($h = 0.5$, $t = 0.1$, $s = 0.1$, $d = 0.2$). Internal equilibrium is $\bar{y} = 0.25$, $\hat{x}_f = 0.75$, $\hat{x}_m = 0.73$.

librium is susceptible to the introduction of any new X_d chromosome exhibiting a reduced viability cost or greater drive. This result is essentially identical to that found by Thomson and Feldman (1975), except that they considered a driver that reduced male fertility. Unless there is a constraint preventing the occurrence of low-cost drivers, a population exhibiting an X/X_d polymorphism should eventually fix for a low-cost X_d chromosome.

A population fixed for X_d and Y (all females are X_dX_d, all males are X_dY) can be invaded by Y_{sup} if its associated viability cost is not too great (Table 2). If Y_{sup} invades, it will go to fixation.

A population fixed for X_d and Y_{sup} (all females are X_dX_d, all males are X_dY_{sup}) will be invaded by X. This is because with Y_{sup} fixed, there is no advantage to X_d because it cannot drive against Y_{sup}. After invading, X will go to fixation.

A population fixed for X and Y_{sup} (all females are XX, all males are XY_{sup}) will be invaded by Y. There is no advantage to Y_{sup} because there are no drivers present. After invading, Y will go to fixation.

I have also analyzed the case in which the Y_{sup} chromosome only partially suppresses drive, such that an X_dY_{sup} male produces $(1/2 + d_s)$ X_d sperm and $(1/2 - d_s)$ Y sperm ($0 \le d_s < d$). If the amount of drive suppression ($d - d_s$) is large relative to its associated viability cost (s), it will invade a population fixed for X_d and Y and go to fixation. With incomplete suppression, the conditions for invasion of the two corner equilibria on the Y_{sup}-fixed edge are the same as for the Y-fixed edge (Table 2) with d_s substituted for d. As with complete suppression, if d_s is small, X will invade a population fixed for Y_{sup} and X_d and go to fixation. For simplicity, I will focus on complete suppression of drive for the remainder of the paper.

Global Behavior

If we assume that there are no constraints governing the occurrence of low-cost drivers (i.e., t can be small) or low-cost suppressors (i.e., s can be small) and that suppressors show complete (or high levels of) suppression, then the edges of the frequency space are unstable (see Fig. 1). What then is the expected behavior of the population? With no stable corner or edge equilibria, an internal equilibrium exists at

$$\hat{y} = \frac{(1 - s)t[(1 - 2h)s + 2hd]}{(2h - 1)s^2t - 2std + 2(1 - ht)d^2}, \tag{7}$$

$$\hat{x}_f = \frac{2d - s}{2d}, \quad \text{and} \tag{8}$$

$$\hat{x}_m = \frac{(s - 2d)[(1 - h)st - d(1 - ht)]}{(1 - 2h)s^2t - 2(1 - 2h)std + 2(1 - ht)d^2} \tag{9}$$

(Clark 1987, eq. 26). The characteristic equation associated with this equilibrium can be determined and simplifies to

$$\begin{aligned}
&2\lambda^3(1 - s)d^2[ts^2(1 - 2h + ht) - 4(1 - h)std + 4(1 - ht)d^2] \\
&\quad - 2\lambda^2(1 - s)d^2[ts^2(3 - 6h + ht + 2h^2t) \\
&\quad - 4ts(2 - 3h + h^2t)d + 2(3 - 4ht + h^2t^2)d^2] \\
&\quad + 4\lambda(1 - s)t(1 - ht)(s - d)d^2[s(1 - 2h) + 2hd] \\
&\quad + 4(1 - h^2t^2)d^4 + (1 - 2h)s^4t^2[1 + 2d - 2h(1 + d)] \\
&\quad - 4sd^3[t + d - 2htd + ht^2(1 + hd)] \\
&\quad + 4s^2td^2[2d + h^2t(4 + 3d) - h(t + 3d + 2td)] \\
&\quad - 2(1 - 2h)s^3td[d + t(1 + 2d - 4h - 3hd)] = 0.
\end{aligned} \tag{10}$$

The roots of equation (10) give the three eigenvalues associated with the internal equilibrium. Due to the complexity of the characteristic, I used Mathematica (Wolfram Research Champaign, IL) to calculate the eigenvalues for a variety of parameter combinations. When the internal equilibrium exists, the leading eigenvalue is complex. When h is small, the modulus of the leading eigenvalue is often less than one in magnitude, indicating that the population will show a spiral approach to the equilibrium (Fig. 2a). As h increases, such that the viability effect of X_d becomes more dominant, the

modulus of the leading eigenvalue becomes greater than one in magnitude and the equilibrium is unstable or shows limit cycles (Fig. 2b). The expected dynamics for three levels of dominance are shown in Figure 3. Note that the region of the parameter space in which an internal equilibrium exists (regions IV and V in Fig. 3) occurs when both *t* and *s* are not too large. As *h* decreases, the internal equilibrium is more likely to be stable (Fig. 3).

When the internal equilibrium is unstable, the population will show cycling away from the equilibrium until it hits an edge (loss of one chromosome type) and then a corner (loss of another chromosome type). With no reintroduction of lost chromosomes, the population will remain at a corner fixation, with one X and one Y chromosome type fixed. However, if chromosomes appear again due to mutation, or if the population is so large that chromosomes are never completely lost, then the population will cycle along the edges.

Cycling along the edges proceeds in the following manner: A population fixed for X and Y is invaded by a (low-cost) driver, which sweeps to fixation, resulting in an X_d, Y population. The X_d, Y population is then invaded by a (low-cost) suppressor resulting in a X_d, Y_{sup} population. The X_d, Y_{sup} population is then invaded by a nondriving X, resulting in an X, Y_{sup} population. Finally the X, Y_{sup} population is invaded by a susceptible Y resulting in an X, Y population. The cycle then repeats. Cycling along the edges requires that chromosomes lost from a population are introduced again later. Populations that cycle would exhibit large changes in the sex ratio. During the course of a complete cycle, the female/male sex ratio at birth would vary between $(1/2 + d)/(1/2 - d)$ and one.

Four-Chromosome Polymorphism

From the above analysis, it is clear that for many combinations of biologically reasonable parameters (*s*, *t* and *h* small), a stable four-chromosome equilibrium is predicted. However, the analysis also predicts the occurrence of chromosome cycling (Fig. 3, region IV). Why then don't we see populations that cycle in nature? There are five possibilities.

First, there is an absence of studies that resample the same population often enough and on a long enough time scale to have noticed fluctuations in the frequency of the sex chromosomes. Carvalho and Vaz (1999) did report essentially no change in the frequency of X_d in two samples 10 years apart. However, we do not know whether the sex ratio was constant in the intervening years.

Second, it is possible that mutation to new sex chromosomes occurs extremely infrequently, in which case the cycle period would be very long. Under this scenario, populations should typically be fixed for an X or X_d chromosome and for a Y or Y_{sup} chromosome (at one of the corners in Fig. 1).

Third, evolution at autosomal loci may prevent driving sex chromosomes from cycling. The model presented here does not address this possibility. Evolution at autosomal loci may also preclude the development of a four-chromosomes equilibrium. Additional theory to test this possibility is needed.

Fourth, low-cost drivers (X_d chromosomes with small *t*) and/or suppressors (Y_{sup} with small *s*) may not exist. In *D. pseudoobscura* the cost of X_d is quite high in females and, in addition, drivers reduce fertility in males (Edwards 1961; Curtsinger and Feldman 1980; Wu 1983). With such high cost drivers, we might predict an X-chromosome polymorphism and possibly a four-chromosome polymorphism, depending on the values of the parameters (Clark 1987; Jaenike 1999).

The Role of Migration in Damping Cycles

The fifth reason why cycling is not seen in nature is that migration may play a role in damping unstable cycles. To investigate this possibility, I extended the model to include two populations that exchanged individuals just prior to mating. Migration between these two populations was assumed to be symmetric such that a fraction *m* of the populations are exchanged.

If the two populations have identical parameter values associated with the four sex chromosomes, they rapidly come into phase with one another, if they start with different chromosome frequencies, and exhibit identical behavior. The behavior seen is that predicted from the single population analysis and is independent of the migration rate.

I next considered the scenario in which the populations differed in the parameters associated with the sex chromosomes. I assumed that the parameter differences were due to variation in the environment and not to genetic variation. For example, one population might reside in a more benign environment and thus the viability effects of the driving X chromosome are less (*t* smaller) than in the more challenging environment of the other population. Alternatively, one environment might be warmer than the other, perhaps exacerbating the effect of the driving X chromosome (*d* larger).

With migration, I have been unable to analytically solve for the location or stability of the internal equilibria. However, numerical iteration of the full recursion system has identified some interesting behavior. In particular, parameter values that result in unstable cycles in both populations with no migration can give stable four-chromosome equilibria with migration. To obtain this result, two conditions are required.

First, at least one of the parameters of drive or viability effect must differ between the two populations. This guarantees that the unstable interior equilibrium will be different in the two populations and that the period of cycling around the equilibrium will differ. Second, the rate of migration must occur within a certain range: too low and it has essentially no effect, too high and the two populations cycle in synchrony. The range of migration rates leading to a stable equilibrium can be quite broad.

Figure 4 illustrates the effect of migration on two populations that differ only in the viability cost of the Y_{sup} chromosome. In that example, migration rates as low as 0.003 and as high as 0.30 result in oscillations that damp to a stable four-chromosome equilibrium. For intermediate migration rates, damping occurs within about 200 generations. Notice that with small *m*, damping occurs such that each population goes to an equilibrium that is close to its original equilibrium in the absence of migration. As *m* increases, the equilibria in the two populations become more similar to one another.

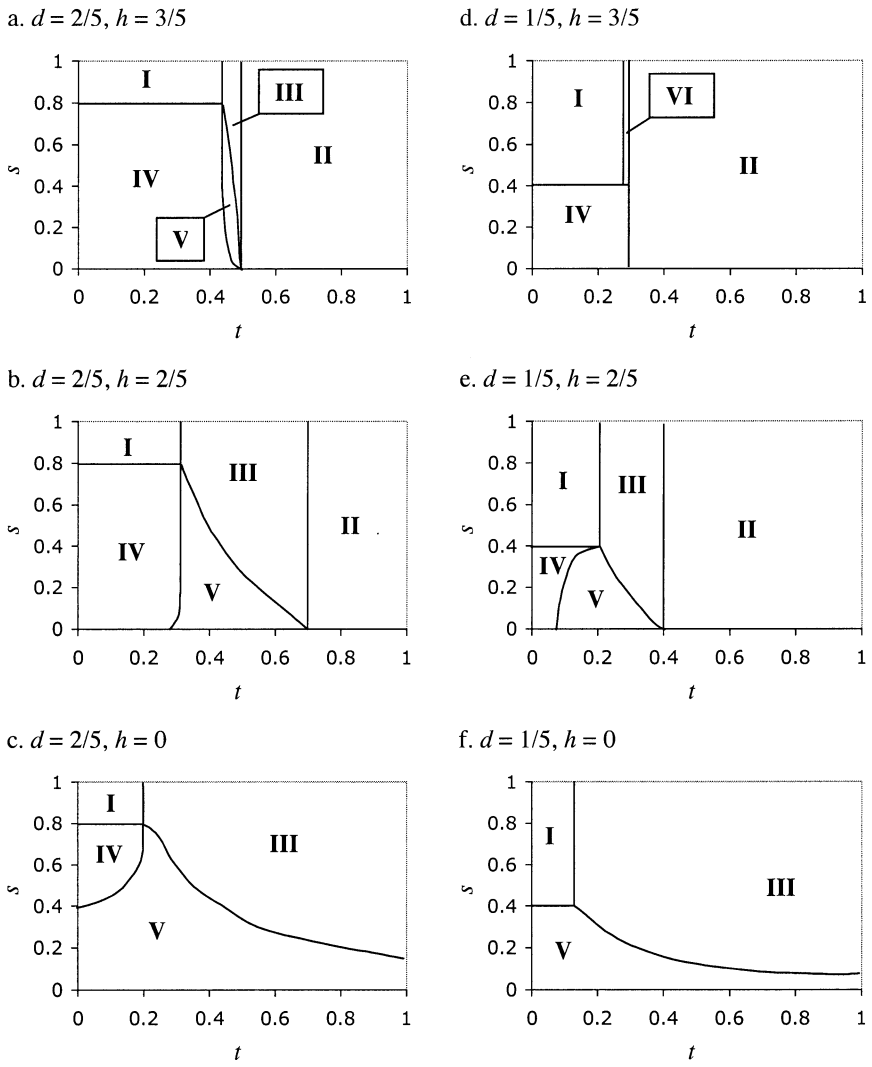

FIG. 3. Predicted dynamics as a function of the viability costs, t and s, of X_d and Y_{sup}, respectively, for three levels of dominance of the viability cost of X_d and two levels of drive. Six different dynamics are shown: (I) stable fixation of both X_d and Y chromosomes (a corner equilibrium); (II) stable fixation of X and Y chromosomes (a corner equilibrium); (III) stable X, X_d polymorphism and fixation of Y (an edge equilibrium); (IV) unstable cycling or limit cycling around a four-chromosome internal equilibrium; (V) stable four chromosome internal equilibrium (X, X_d, Y, and Y_{sup} present at equilibrium); and (VI) unstable X, X_d edge equilibrium (fixed for Y) in which the population can become fixed for X or X_d, depending on starting chromosome frequencies.

In the example in Figure 4, with $m = 0.35$ the two populations show stable cycles around equilibria which are very similar (Fig. 4). With $m = 0.5$, the two equilibria are identical (and show instability) because the two populations have become one.

In every case examined, populations with different innate periods of unstable cycling show increased stability, usually exhibiting a stable four-chromosome equilibria, but occasionally showing limit cycles, with certain levels of migration.

DISCUSSION

Populations exhibiting sex-linked meiotic drive are expected to show edge instability as long as drivers and suppressors have low viability costs associated with them. This edge instability guarantees the existence of an internal equilibrium that can be stable or unstable (Fig. 3, regions IV and V). Thus two behaviors are expected in natural populations: a stable four-chromosome equilibrium and cycling of sex chromosomes along the edges.

The absence of cycling in nature may be explained by the occurrence of migration between populations possessing slightly different drive and viability parameters. Because many of the species possessing sex-linked drivers and modifiers are in organisms with high dispersal ability (dipterans), migration among populations seems a reasonable hypothesis. The occurrence of populations exhibiting (stable) frequencies of X, X_d, Y, and Y_{sup} chromosomes may thus be best explained by migration between populations that would otherwise exhibit unstable cycling of sex chromosomes.

Previous studies have focused on the X/X_d polymorphic equilibrium as the explanation for populations exhibiting

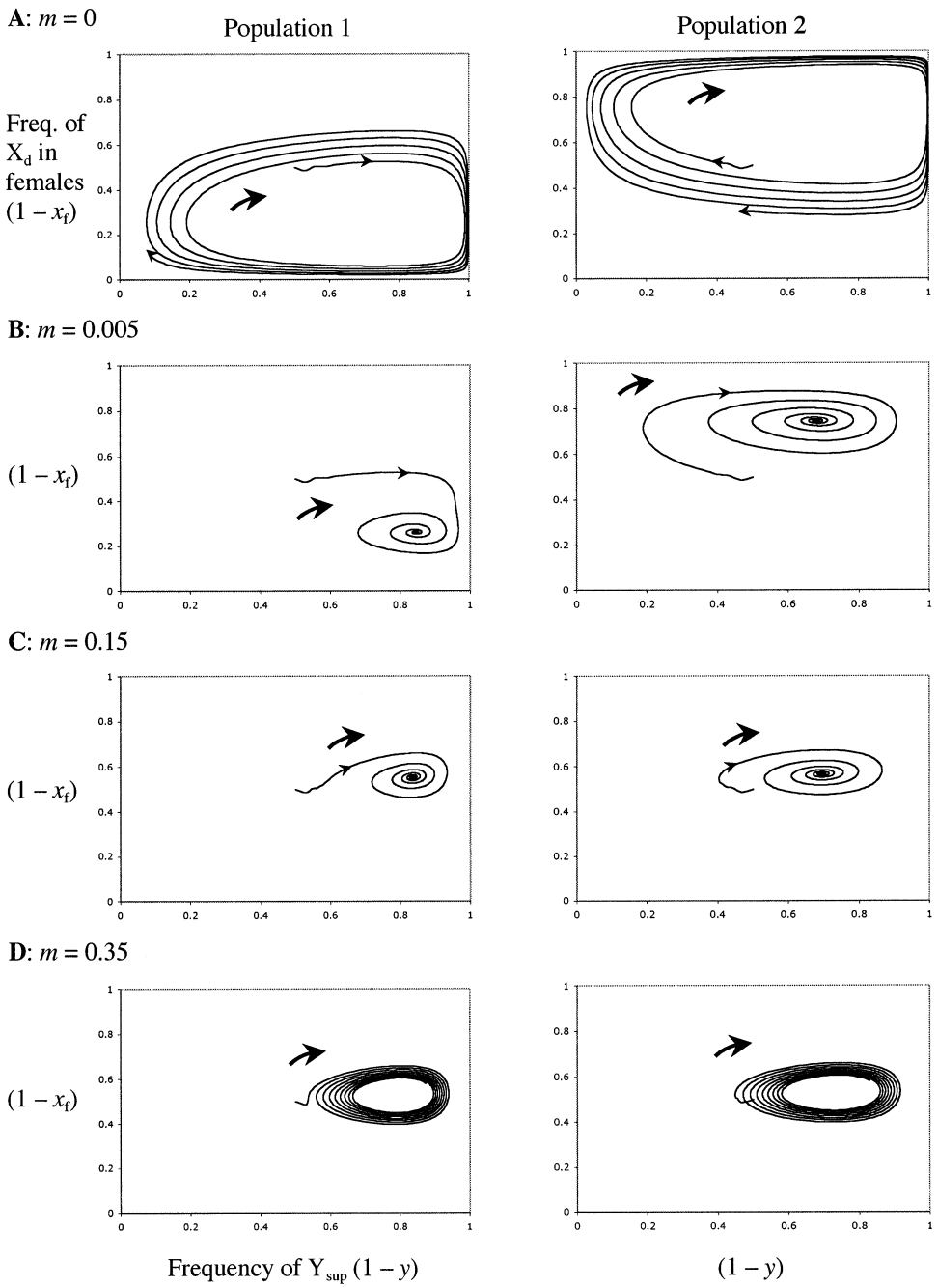

FIG. 4. The effect of migration between two populations exhibiting unstable cycling. Population 1 has parameters $h = 0.5$, $t = 0.1$, $s = 0.1$, $d = 0.2$ with an internal equilibrium at $\hat{y} = 0.25$, $\hat{x}_f = 0.75$, $\hat{x}_m = 0.73$ with no migration. Population 2 has parameter $h = 0.5$, $t = 0.1$, $s = 0.3$, $d = 0.2$ with an internal equilibrium at $\hat{y} = 0.22$, $\hat{x}_f = 0.25$, $\hat{x}_m = 0.23$ with no migration. Populations were started with equal frequencies of all four chromosomes and followed for 1000 generations.

polymorphism (Edwards 1961; Curtsinger and Feldman 1980; Clark 1987; Hurst and Pomiankowski 1991). Populations that reach this equilibrium are highly susceptible to invasion by low-cost drivers (Thomson and Feldman 1975). Thus, this equilibrium is likely to be transient, unless there is a constraint on the evolution of low-cost drivers.

It would be of interest to ascertain whether autosomal suppressors, perhaps with their own fitness-reducing effects, would invade a population at a four-chromosome equilibrium. If likely, this might explain why sex-linked drivers are not observed that frequently in nature.

Cycling has been observed in analyses of systems involving selfish elements besides sex-ratio meiotic drive. In a study of autosomal meiotic drive, Charlesworth and Hartl (1978) found cyclic dynamics in their analysis of the population genetics of the *Drosophila* segregation distortion phenotype. Underlying this phenotype are two loci, *segregation distorter* and *responder*. The two loci are tightly linked. The *Sd* allele

at the segregation-distorter locus produces a protein that is toxic to sperm, while the *Rsp* allele at the responder locus confers some resistance to the toxin. A driving chromosome has genotype *Sd Rsp* and produces approximately 95% *Sd Rsp* sperm when in a *Sd Rsp*/__*Rsp*$^+$ male. A resistant chromosome has genotype *Sd*$^+$ *Rsp*. For some parameter combinations, Charlesworth and Hartl (1978) noted that a population would approach a stable internal equilibria in an oscillatory fashion. For some other parameter combinations, they predicted cycling around an unstable internal equilibrium. Oscillations were due to the increase in the driver (*Sd Rsp*) followed by an increase in the resistant chromosome (*Sd*$^+$ *Rsp*), followed by a decrease in the (costly) driver and subsequent decrease in the (costly) resistant chromosome (Charlesworth and Hartl 1978).

Hurst and McVean (1996) observed cyclic dynamics in the population genetics of cytoplasmic incompatibility (CI). In their model, based on the endosymbiont *Wolbachia* system, the host species possessed three cytoplasmic types. Hosts were either uninfected or infected by one of two types of endosymbiont, one that produced a toxin in sperm or one that did not. The toxin was assumed to kill uninfected zygotes (CI), but not infected ones. Infection by either endosymbiont type was costly to the host, and production of the toxin added an additional cost. Hosts were thus sensitive (uninfected), CI-inducing (infected by a toxin-producing endosymbiont), or resistant (infected by a endosymbiont that lacks the toxin). Both CI-inducing and resistant endosymbionts were vertically transmitted to progeny at the same rate. Populations of sensitive hosts were susceptible to spread of CI-inducing hosts. Populations of CI-inducing hosts were susceptible to the invasion and spread of resistant hosts. Populations of resistant hosts were in turn susceptible to the invasion and spread of sensitive hosts.

It is possible that the cyclic dynamics predicted for segregation distortion, cytoplasmic incompatibility and perhaps other systems would be replaced by stable equilibria in the presence of migration, similarly to sex-ratio meiotic drive.

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